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Antibiotics in Urology – New Essentials

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Urinary tract infections (UTIs) are one of the most common reasons that adults seek medical and urologic consultation and are one of the most frequently occurring nosocomial infections [1–4]. In urology, nosocomial UTIs are almost exclusively complicated UTIs (ie, UTIs associated with structural or functional abnormalities of the urinary tract, with a broad spectrum of etiologic pathogens) [5]. Empirical antimicrobial therapy in urology must be instigated on occasions when urosepsis is pending or the general condition is deteriorated and is likely to improve significantly by the immediate use of antimicrobial agents [6]. For rational empiric therapy it is necessary to consider the bacterial spectrum and antibiotic susceptibility of uropathogens. Because spectrum and resistance rates may vary from time to time, area to area, and hospital to hospital, each institution must be able to provide its own local evaluation. On the other hand, antibiotics also frequently are prescribed empirically in situations in which patients do not want to wait for the results of the susceptibility testing because of their highly bothersome symptoms (eg, acute uncomplicated cystitis) [7].

Bacterial spectrum and antimicrobial resistance in urinary tract infections

Uncomplicated urinary tract infection

In uncomplicated UTIs, *Escherichia coli* is the most common pathogen, typically being isolated from more than 80% of outpatients with acute uncomplicated cystitis across various regions of the world [7]. *Staphylococcus saprophyticus* accounts for 5% to 15% of these infections and is especially prevalent in younger women who have cystitis. Causative pathogens in the remaining 5% to 10% of cases include aerobic gram-negative rods, such as *Klebsiella* and *Proteus* spp, and enterococci. The range of pathogens associated with acute uncomplicated pyelonephritis is similar to that seen in acute uncomplicated cystitis [8].

The North American Urinary Tract Infection Collaborative Alliance study from 2003 and 2004 determined resistance rates in *E coli*. Resistance to ampicillin was 38%, 21% to trimethroprim/sulfamethoxazole, 1% to nitrofurantoin, and 6% to ciprofloxacin [9]. The ARESC Project, an international surveillance study that involved nine countries in Europe and Brazil, monitored antimicrobial susceptibility of uropathogens from 2004 to 2006. The aim of the study was to rank the current usefulness of drugs used in the therapy of this condition [10]; 3018 uropathogens, including 2315 *E coli* pathogens (76.7%), 322 other gram-negative pathogens (10.7%), and 406 gram-positive pathogens (13.5%) were evaluated. Susceptibility in *E coli* was less common towards ampicillin (mean 41.1%; range 32.6%–60.8%), cotrimoxazole (70.5%; 54.5%–87.7%), and cefuroxime (81.0%; 74.5%–91.3%). Ciprofloxacin susceptibility was 91.3%, but the figures for Spain and Italy were substantially lower (88.1% and 87.0%, respectively). Fosfomycin, mecillinam, and nitrofurantoin were the agents with the highest susceptibility rates (98.1%, 95.8%; and 95.2%, respectively).

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Complicated urinary tract infection

The bacterial spectrum of complicated, nosocomial UTI is much more heterogeneous and comprises a wide range of gram-negative and -positive species. In the latest report from the SENTRY antimicrobial surveillance program 2000, the bacterial spectrum of hospitalized urologic patients in North America consisted of 47% *E coli*, 13% *Enterococcus* spp, 11% *Klebsiella* spp, 8% *Pseudomonas* spp, 5% *Proteus mirabilis*, 4% *Enterobacter* spp, and 3% *Citrobacter* spp (less frequently isolated species not mentioned) [11]. Antibiotic resistance in *E coli* for ampicillin was 37%, 4% for ciprofloxacin, and 23% for trimethoprim/sulfamethoxazole; in *Pseudomonas aeruginosa* resistance for ciprofloxacin was 29%. Vancomycin resistance in *Enterococcus* spp was 7%, and the presence of extended-spectrum β-lactamase in *E coli* was 4% and 19% in *Klebsiella* spp.

Antibiotic substances for the treatment of urinary tract infection

To affect the bacterial cell, probably all antibiotics must get into the cell. Antimicrobial substances used for the treatment of UTI can be distinguished from those that act on the bacterial DNA, those that inhibit protein synthesis, and those that inhibit peptidoglycan synthesis. The way in which urologically important antibiotics work is alluded to in the following section.

Antibiotics that act on the DNA

Fluoroquinolones act directly on the bacterial DNA. The target structures are the bacterial topoisomerases II and IV, which introduce so-called negative "supercoils" into DNA and achieve a higher order by coiling. Four molecules of the quinolone substance form a ternary complex together with topoisomerases and DNA, which causes DNA double-strand breakage [12,13].

Sulfonamides, such as sulfamethoxazole, lead to the formation of ineffective forms of tetrahydrofolate (dihydropteroic acid) from para-aminobenzoic acid and pteridine by substituting para-aminobenzoic acid. Tetrahydrofolate physiologically is further catalyzed to dihydrofolic acid (folate), which is further catalyzed into tetrahydrofolic acid by dihydrofolate-reductase.

Pyrimethamines, such as trimethoprim, competitively inhibit the bacterial dihydrofolate-reductase. Purine synthesis is inhibited [13].

Antibiotics that inhibit protein synthesis

The aminoglycosides bind irreversibly to distinct parts of the 30S and 50S subunits of the bacterial ribosomes. Consequently, the amino acid translocation is inhibited by preventing the binding of elongation factor G. The elongation stage in bacterial translation is inhibited [13]. Oxazolidinones bind to the 23S rRNA of the 50S subunit of the bacterial ribosomes and inhibit the formation of the 70S initiation complex. The initiation stage of bacterial translation is inhibited [13].

Antibiotics that inhibit peptidoglycan synthesis

β-Lactams inhibit the last stage of peptidoglycan synthesis. They bind to penicillin-binding proteins (PBP), which act as enzymes (eg, transpeptidases, carboxypeptidases, and endopeptidases) in the formation and preservation of parts of the bacterial cell wall. The affinity of distinct penicillins for certain PBPs might be different. Penicillins inhibit the process of cross-linking of the long polysaccharide chains by short polypeptides. They are analogous substrates of the acyl-D-alanyl-D-alanine moieties and acylate transpeptidases. Consequently, the peptidoglycan wall is weakened [13]. The glycopeptide antibiotics bind to the acyl-D-alanyl-D-alanine moieties and inhibit the process of transglycosilation of the peptidoglycan wall [13].

Fosfomycin acts as an analog of phosphoenolpyruvate and forms a covalent bond with the active site cysteine residue (Cys 115) of UDP-N-acetylglucosamine enolpyruvyltransferase (MurA), which is a key enzyme of peptidoglycan synthesis [14]. It inhibits cell wall synthesis other than β-lactam antibiotics.

Mechanisms of antibiotic resistance in uropathogens

Antibiotic resistance is defined if bacteria can still grow under achievable therapeutic concentrations of antibiotic substances at the site of infection. Resistance is classified into (1) primary or inherent resistance of bacteria if bacteria are constitutively resistant against an antibacterial substance and (2) secondary or acquired resistance if resistance emerges in intrinsically susceptible bacteria. Epidemiologically important is transferable resistance located on plasmids (extrachromosomal autonomous mobile genetic element transferable to other cells) or transposons

(chromosomal mobile genetic element transposable to plasmids or other chromosomal sites).

Alterations of permeability and efflux mechanisms

Intrinsic resistance of gram-negative bacteria against macrolides is caused by impermeability of the outer membrane to these hydrophilic compounds. *Enterococcus* spp show decreased permeability toward aminoglycosides and are intrinsically low level resistant to aminoglycosides. On the other hand, permeability can be altered by altered production of outer membrane proteins (eg, *E coli)*, leading to decreased susceptibility to fluoroquinolones or β-lactam antibiotics.

Efflux mechanisms potentially can pump antibiotic substances, such as quinolones or tetracyclines, out of the cell. Thus far, five superfamilies of efflux transport systems are known: ATP-binding cassette (ABC), major facilitator superfamily (MFS), resistance-nodulation division (RND), small multidrug resistance (SMR), and multidrug and toxic compound extrusion (MATE) families. Efflux systems are responsible for low-level resistance and may promote selection of mutations responsible for higher level resistance [15].

A powerful efflux mechanism in *Pseudomonas* spp is one constitutively produced system (MexAB-OprM: RND superfamily) that generates intrinsic resistance against most β-lactams, quinolones, tetracycline, chloramphenicol, trimethoprim, and sulfamethoxazole. On the other side, nonconstitutive systems (ie, MexCD-OprJ, MexEF-OprN) can be expressed by mutation. In other species, such as *Staphylococcus aureus*, coagulase-negative staphylococci, or *Citrobacter freundii,* efflux is also an important mechanism of clinical resistance against quinolones [16–19].

Alterations of target structures

Target structures can be altered by mutations, acquisition of genetic material, or inactivation of antibiotics by enzymatic modification [13].

Mutations

Fluoroquinolone resistance is mediated by target modifications (DNA gyrase and/or topoisomerase IV) and decreased intracellular accumulation [16]. Although in gram-negative bacteria (eg, *E coli*) the DNA-gyrase is the primary target, in gram-positive bacteria (eg, *S aureus*) topoisomerase IV is the primary target for some but not all quinolones [17]. With clinically relevant concentrations, newer quinolones such as moxifloxacin and gemifloxacin inhibit both targets—the DNA-gyrase and topoisomerase IV.

Ampicillin resistance in enterococci is associated with overproduction of a low-affinity PBP, which is called PBP-5. High-level ampicillin resistance in *Enterococcus faecium* is associated with intrinsic overproduction of a modified PBP-5 that further lowers the penicillin-binding capability [20]. Vancomycin resistance in enterococci is caused by the manufacture of a peptidoglycan side chain from D-alanyl-D-lactate, which is incorporated into the peptidoglycan cell wall instead of the vancomycin target D-alanyl-D-alanyl. The D-alanyl-D-lactate chain shows dramatically lowered affinity to vancomycin. Vancomycin resistance is conferred by five genes located on a transposable element [21].

Acquisition of genetic material

Resistance to TMP/SMZ arises from various mechanisms that involve enzyme alteration, cellular impermeability, enzyme overproduction, inhibitor modification, or loss of binding capacity. The mechanism of greatest clinical importance is the production of plasmid-encoded, trimethoprim-resistant forms of dihydrofolate reductase [22–24]. Resistance in methicillin-resistant *S aureus* is mediated by an additional PBP-2a, which has unusually low affinity for all β-lactam antibiotics. PBP-2 and PBP-2a belong to a family of bifunctional proteins with an N-terminal transglycosylase and C-terminal transpeptidase domain. In case of blockage of PBP-2 by β-lactam antibiotics, PBP-2a takes over the enzymatic activity. PBP-2a is encoded by a *mecA*-gen that has been incorporated into the chromosomal DNA of *S aureus* and coagulase-negative staphylococci strains [25].

Inactivation of antibiotics

β-Lactamases are enzymes produced by bacteria that inactivate β-lactam antibiotics by cleavage of the β-lactam ring. More than 200 different enzymes have been identified thus far, and the substrates comprise penicillins, cephalosporins, or other β-lactam antibiotics. Resistance to penicillin is mediated by a penicillinase that hydrolyses the β-lactam ring of penicillin. More than 90% of *S aureus* isolates are penicillinase producers. This resistance can be overcome with penicillinase-stable penicillins, such as oxacillin [25]. A frequent resistance mechanism in *E coli* and *Proteus* spp is production of TEM-1, a plasmid-mediated β-lactamase that is inhibitor resistant [26]. It confers

resistance in strains that have acquired the resistance plasmid (eg, to ampicillin and ampicillin/sulbactam).

The SHV-1 β-lactamase of *Klebsiella pneumoniae* and the K1 β-lactamase of *Klebsiella oxytoca* are chromosomally encoded but inhibitor sensitive [27]. It encodes intrinsic resistance in all *Klebsiella* strains, for example, to ampicillin but not to ampicillin/sulbactam. *Enterobacter* spp possess a chromosomally encoded ampC β-lactamase that inactivates penicillins and cephalosporins and is not inhibitor sensitive. Resistance, however, results only if the β-lactamase is hyperproduced. Ampicillin is a strong inducer of this enzyme. Mezlocillin is less suitable to induce hyperproduction of this β-lactamase [28].

The genus *Citrobacter* comprises such species (*Citrobacter freundii* group) that behave like *Enterobacter* spp and those that produce other less extended β-lactamases (*Citrobacter koseri*/*diversus*). In *Proteus* spp, a wide diversity of β-lactamases can be produced, serving as a possible β-lactamase–encoding reservoir [28,29]. Plasmid-encoded, extended-spectrum β-lactamase production is important in *K pneumoniae*, *E coli*, *Proteus* spp, and *C diversus*. Other resistances, such as aminoglycoside and trimethoprim-sulfamethoxazole resistance, are often cotransferred on the same plasmid [30].

Enterobacter spp, *C freundii*, *Serratia* spp, *K oxytoca*, *M morganii,* and *Providencia* spp possess a chromosomally encoded β-lactamase that can be induced to hyperproduction by mutation or depression [31]. This hyperproduced β-lactamase also causes a resistance phenotype, comparable to extended-spectrum β-lactamase, although no extended-spectrum β-lactamase is produced. Other inactivating enzymes can inactivate aminoglycosides or macrolides. The expression of a bifunctional aminoglycoside inactivating enzyme, 6′-N-aminoglycoside acetyltransferrase-2′-O-aminoglycoside phosphotransferase, is the most important mechanism of high-level aminoglycoside resistance in *Staphylococcus* spp and *Enterococcus* spp [32]. Enterococci are intrinsically low-level resistant; in the case of high-level resistance, aminoglycoside combination therapy would be ineffective.

Among *Enterobacteriaceae,* combinations of gentamicin-modifying enzymes are common. In *Pseudomonas* spp the combination of gentamicin-modifying enzymes and decreased permeability is common [33]. Bacteria exhibit an enormous repertoire of different resistance mechanisms. Unspecific mechanisms, such as reduced permeability or efflux, alter the tolerance to antibiotic substances less than specific mechanisms, such as inactivation of the antibiotic. The antibiotic spectrum targeted is much more extensive, however. On the other hand, unspecific mechanisms also can be induced by nonantibiotic substances, such as salicylates. Low-level resistance can be conferred and give bacteria a selection advantage.

Therapy of uncomplicated urinary tract infection

The results of the studies performed in the field of uncomplicated UTI show that antibiotic substances classically used for the treatment of uncomplicated UTI, such as cotrimoxazole, fluoroquinolones, and aminopenicillins, lose their effectiveness because of increasing resistance. Ideal substances are those with low resistance rates used exclusively for this indication, such as fosfomycin tromethamine, nitrofurantoin, and pivmecillinam.

Fosfomycin

Fosfomycin tromethamine is the oral applicable salt of fosfomycin. Fosfomycin (cis-(1R,2S)-epoxypropylphosphonic acid) is an oxirane antibiotic unrelated to other substances and is produced as a secondary metabolite by *Streptomyces* and *Pseudomonas* spp [14]. (S)-2-hydroxypropylphosphonic acid epoxidase catalyzes the epoxide ring closure of (S)-2-hydroxypropylphosphonic acid to form fosfomycin in an iron-redox mechanism [34]. Hydroxypropylphosphonic acid epoxidase represents a new subfamily of non-haem mononuclear iron enzymes that respond to its substrates with a conformational change that protects the radical-based intermediates formed during catalysis [35]. Fosfomycin is active against gram-positive and -negative bacteria but shows decreased activity against *Morganella morganii*, *Proteus vulgaris*, *P aeruginosa,* and *E faecium*. Despite many years of use, fosfomycin continues to be characterized by a low incidence of *E coli*–resistant strains (1%–3%) worldwide [36]. Fosfomycin trometamol has retained its activity against quinolone-resistant strains of *E coli,* and cross-resistance with other classes of antimicrobial agents is currently not a problem [37]. It is less active against coagulase-negative staphylococci. A meta-analysis of 2048 patients showed that overall single-dose therapy with fosfomycin trometamol exhibits equivalent results as short-term therapy with comparative agents, however [38].

Fosfomycin trometamine has approximately 40% oral bioavailability [39], and urine recovery is approximately 40% [40].

Nitrofurantoin

Nitrofurantoin belongs to the nitroheterocyclic compounds. The nitrogroup coupled onto the heterocyclic furan ring represents the proper site of effect. The nitrogroup is inactive and must be activated by microbial nitroreductases after penetration into the microbial cell [41]. Nitrofurantoin interferes with carbohydrate metabolism. The antibacterial activity is generally weak, but in urine the activity against *E coli* and some other enterobacteria, such as like *Klebsiella* spp and *Enterobacter* spp, is sufficient in the treatment of uncomplicated UTI. There is no activity against *Proteus* spp or *P aeruginosa*. Low levels of resistance to nitrofurantoin among uropathogens (*E coli* <2%) has revived interest in this agent. In women at risk for infection with resistant bacteria or in the setting of a high prevalence of TMP-SMX–resistant uropathogens, nitrofurantoin also can be used. Its use for the empiric treatment of uncomplicated cystitis is supportable from a public health perspective in an attempt to decrease uropathogen resistance because it does not share cross-resistance with more commonly prescribed antimicrobial agents [42], but short-term therapy is not well established with nitrofurantoin [43]. It is also less active against gram-negative pathogens other than *E coli*. Urinary excretion is 40% [40].

In a multicenter clinical trial, single-dose fosfomycin tromethamine, 3 g, was compared with a 7-day course of nitrofurantoin monohydrate/macrocrystal, 100 mg, for the treatment of acute uncomplicated lower UTI in female patients [44]. Seven hundred forty-nine patients were enrolled in the study (375 received fosfomycin and 374 received nitrofurantoin). Overall, 94% of pretreatment isolates were susceptible to fosfomycin and 83% were susceptible to nitrofurantoin. Bacteriologic cure rates at 5 to 11 days after initiation of treatment were 78% and 86% for fosfomycin and nitrofurantoin, respectively ($P = .02$). 1 week after treatment they were 87% and 81% for fosfomycin and nitrofurantoin, respectively ($P = .17$). Clinical success rate (cure and improvement) was higher than 80% in both treatment groups. Bacteriologic and clinical cure rates were comparable in both treatment groups [44].

Pivmecillinam

Pivmecillinam is a unique β-lactam antimicrobial agent that has been used for the treatment of acute uncomplicated UTI for more than 20 years. Pivmecillinam is the pro-drug (ester) of mecillinam with specific and high activity against gram-negative organisms such as *E coli* and other *Enterobacteriaceae*. Mecillinam is an amidine derivative of the penicillin group. Pivmecillinam is also well absorbed orally [45]. Since its introduction it has been used widely for the treatment of acute uncomplicated cystitis, primarily in the Nordic countries. The level of resistance has remained low; approximately less than 2% of *E coli* community isolates are resistant to mecillinam [46]. A comparative study (pivmecillinam versus norfloxacin) showed similar outcomes with 7 days of pivmecillinam, 200 mg, twice daily or 3 days of norfloxacin, 400 mg, twice daily when pooling bacteriologic outcomes from two studies [47]. The in vitro minimal inhibitory concentration for *S saprophyticus* is 8 to 64 mg/L, so these bacteria are considered resistant. The cure rates for this organism were reported between 73% and 92%, however. Pivmecillinam can be considered effective for treatment of cystitis caused by *S saprophyticus* [47].

Nicolle and colleagues [48] evaluated the efficacy of a 3-day regimen of pivmecillinam, 400 mg, twice daily versus norfloxacin, 400 mg, twice daily in 954 premenopausal women with symptoms of acute cystitis. Bacteriologic cure at early posttherapy follow-up was achieved in 75% of patients who took pivmecillinam and 91% of patients who took norfloxacin ($P < .001$). Clinical cure/improvement 4 days after initiation of therapy was observed in 95% of women who received pivmecillinam and 96% who received norfloxacin ($P = .39$). In women younger than 50 years, early clinical cure rates were 84% for pivmecillinam and 88% for norfloxacin ($P = .11$). Adverse effects were similar for both regimens, and there was no evidence of the emergence of increasing resistance with therapy. The authors concluded that short-course therapy with norfloxacin was superior to that with pivmecillinam in terms of bacteriologic outcome; however, clinical outcome in young women was comparable [48].

Therapy of complicated urinary tract infection

In most studies about complicated UTI, increasing rates of antibiotic resistance were found

with specific species such as *E coli, P aeruginosa*, *Klebsiella spp, Enterobacter spp*, enterococci, and staphylococci. Extended-spectrum β-lactamases that produce *E coli* and *K pneumoniae* rapidly increase and may cause significant clinical problems in the treatment of UTI [49,50]. Although from a hygienic point of view they are regarded as not as dangerous as plasmid-encoded β-lactamases, species that produce chromosomally encoded β-lactamases also pose significant clinical problems for empiric antibiotic therapy.

Antibiotic substances with novel mode of action and effective against gram-negative pathogens are scarce. Glycylcyclines may be a new development forward; however, the currently marketed drug tigecycline is not aimed for treatment of UTI because of limited urinary excretion. In the light of these developments, old established substances, such as polymyxins, chloramphenicol, tetracycline, and temocillin, regain interest in situations in which multiply antibiotic-resistant pathogens appear. On the other hand, carbapenems still retained their activity in most of the uropathogens and are currently widely developed for treatment of complicated UTI.

Carbapenems

Carbapenems are currently available only intravenously because they are unstable, especially in gastric juice or intestinal juice. The available carbapenems are currently classified by different criteria. The classification by groups can follow the bacterial spectrum as in other antibiotic classes [51]. According to that classification, ertapenem is the sole representative of the first group and imipenem and meropenem are the representatives of the second group, which are currently licensed in Europe. Carbapenems are active against gram-positive and -negative pathogens and anaerobic pathogens. Carbapenems maintain antibacterial efficacy against most β-lactamase–producing organisms. This stability against serine-β-lactamases is caused by the trans-1-hydroxyethyl substituent and its unique juxtaposition to the β-lactam carbonyl group [52]. The stability encompasses extended spectrum-β-lactamases and AmpC β-lactamases; however, it does not extend to metallo-β-lactamases.

The group one parenteral carbapenem ertapenem has good gram-negative activity, excluding *P aeruginosa*. It is also not active against methicillin-resistant *S aureus* and enterococci. It contains a 1β-methyl substituent that reduces hydrolysis of the β-lactam group by the renal dihydropeptidase I. It further contains a meta-substituted benzoic acid substituent, which increases the molecular weight and lipophilicity of the substance, and a carboxylic acid moiety, which results in a net negative charge. This results in a high protein binding that leads to a longer serum half-life [52]. Urinary excretion is 80% [40].

Group two parenteral carbapenems include imipenem and meropenem, which are active against many gram-positive and -negative uropathogens, excluding methicillin-resistant *S aureus*, *E faecium,* and vancomycin-resistant enterococci. Imipenem is hydrolysed by the renal dihydropeptidase I and is combined with the specific inhibitor cilastatin. Urinary excretion of the active imipenem is 70% if combined with cilastatin. Meropenem contains the 1β-methyl-substituent and is stable against the renal dihydropeptidase I. Compared with imipenem, it is somewhat more active against *P aeruginosa* but less active against gram-positive uropathogens. The urinary excretion of the active substance is 70% [40].

Doripenem is a new parenteral carbapenem and offers slightly more activity than meropenem against selected pathogens, including some—but not all strains—of *P aeruginosa* not susceptible to imipenem or meropenem. Doripenem is also active against gram-positive pathogens except methicillin-resistant *S aureus*, *E faecium,* and vancomycin-resistant enterococci. Urinary excretion is 75% and is of potential interest for the treatment of complicated UTI [53]. A large, multinational phase III study evaluated the efficacy and safety of doripenem for the treatment of complicated lower UTIs and pyelonephritis (complicated and uncomplicated) and compared it to levofloxacin [54]. A total of 753 patients were randomized. The microbiologic cure rate in the test of cure population was 82.1% for doripenem and 83.4% for levofloxacin. The clinical cure rate in the test of cure population was 95.1% for doripenem and 90.2% for levofloxacin. Doripenem was microbiologically and clinically effective and therapeutically noninferior to levofloxacin in this study for the treatment of complicated UTIs and was generally safe and well tolerated [54].

Orally active 1β-methylcarbapenems have been undergoing preclinical or clinical trials for years [55]. Substances CS-834, L-084, and DZ-2640 have been selected for further investigation [55]. CS-834 from Sankyo is the orally active prodrug of the substance R-95,867. The substance is active against gram-positive and -negative species, such as *S aureus*, *E coli,* and *K pneumoniae*, but is less

active against *Pseudomonas* spp and *Enterococcus* spp [56]. The 24-hour cumulative renal excretion into urine in healthy volunteers ranged from 27% to 34% [55]. L-084, which was developed by Wyeth, is the orally active prodrug of L-036. This substance exhibits excellent antibacterial activity against gram-positive and -negative species, with the exception of *P aeruginosa*. The accumulative urinary recoveries in volunteers within 24 hours ranged from 54% to 73% [55]. DZ-2640 from Dai-ichi group exhibits broad antibacterial activity, except for *P aeruginosa*. The cumulative renal recoveries in volunteers ranged between 32% and 45% [55].

Urinary excretions of the oral carbapenems are certainly not optimal but are still in the intermediate range. Exaggerated consumption of carbapenems in the future will certainly lead to the emergence of antibiotic resistance and multiresistant pathogens.

Old antibiotics

The so-called "old antibiotics," such as polymyxins, chloramphenicol, doxycycline, and temocillin, have regained interest because of the need for unrelated substances in multiply-resistant organisms. None of these substances has been investigated in adequate clinical studies for the treatment of UTI, however.

Polymyxins

The increasing incidence of infections caused by multi-drug resistant *P aeruginosa* and the fact that no new antipseudomonal agent will be available in the near future caused renewed interest in the polymyxine antibiotics. Colistin and colistimethate are the only currently available compounds [57]. Colistimethate probably is the nonactive prodrug of colistin, which reacts with phospholipid components of the cytoplasma membrane and increases cell wall permeability. It displays bactericidal activity against *P aeruginosa* and extended-spectrum β-lactamase, producing gram-negative organisms. In a study of patients who had cancer and *P aeruginosa* infections, colistin was as effective and safe as β-lactam antibiotics and fluoroquinolones [58]. Colistimethate is predominantly cleared by the renal route, but a fraction of the administered dose is converted in vivo to colistin. There are some case reports of patients with UTI treated with intravenous colistimethate and good clinical outcomes reported in up to 83%, although no clinical study has been performed [57]. Nephrotoxicity and neurotoxicity are the most common potential toxicities with parenteral administration of colistimethate, which are probably caused by inappropriate dosing. Satisfactory safety profiles have been reported with intravenous doses of 160 mg three times daily in patients with normal renal function [57].

Chloramphenicol

Chloramphenicol is active against gram-positive and -negative pathogens, with the exception of *P aeruginosa*. Resistance in enterobacteria has decreased over the last 15 years, probably because of restricted usage. Renal excretion amounts to 90%. Severe side effects have been reported, including hematologic disturbances, gastrointestinal effects, Gray syndrome, and neurologic effects [40].

Tetracycline

Doxycycline is the best orally resorbed tetracycline. Doxycycline exhibits good activity against most gram-positive bacteria, variable activity against gram-negative pathogens, and no activity against *P aeruginosa*, *Proteus* spp, and *Serratia marcescens*. Urinary recovery rates after intravenous and oral application are 70% and 40%, respectively [40].

Temocillin

Temocillin is a semisynthetic parenteral penicillin that exhibits increased stability against β-lactamases and is active against extended-spectrum β-lactamase–producing organisms. The 24-hour urinary recovery rate was between 66% and 74% of the administered doses (0.5–2 g) in volunteers [59].

Antibiotics active against otherwise resistant gram-positive uropathogens

Daptomycin and linezolid are active exclusively against gram-positive uropathogens, such as enterococci and methicillin-susceptible and -resistant staphylococci. In one study, 529 isolates of uropathogens that caused complicated UTIs were tested against daptomycin and linezolid; no resistant strain was detected [60].

Daptomycin

Daptomycin is a semisynthetic lipopeptide antibiotic with a high specificity for gram-positive bacteria [61,62]. Daptomycin apparently acts via the dissipation of the bacterial membrane potential and has a rapid concentration-dependent bactericidal activity [62]. Daptomycin showed in vitro activity superior to that of vancomycin against methicillin-resistant *S aureus*, methicillin-sensitive

S aureus, methicillin-resistant *Staphylococcus epidermidis,* and vancomycin-resistant enterococci and comparable activity against vancomycin-susceptible *E faecalis* and streptococci [62]. Daptomycin is administered intravenously, serum half-life averaged 8.5 hours, protein binding is approximately 90%, and urinary excretion is 80%, 66% of which is as active drug. Tolerability data are available for 285 patients from two multicenter, randomized phase II trials who received 2 mg/kg every 24 hours for up to 25 days or 3 mg/kg every 12 hours for up to 34 days. Daptomycin was well tolerated at these dosages with no evidence of drug-related toxicity [63]. A series of single- and repeated-dose studies in rodents, dogs, and monkeys demonstrated that the skeletal muscle is the most sensitive target organ for toxicity of daptomycin. The severity of microscopic lesions was dose dependent but did not progress with extended treatment (up to 6 months) and was completely and rapidly reversible upon cessation of dosing [62].

Linezolid

Linezolid is a member of the oxazolidinone class synthetic antibacterial agents that inhibit bacterial protein synthesis through a unique mechanism. In contrast to other inhibitors of protein synthesis, linezolid acts early in translation by preventing the formation of a functional initiation complex [64]. Linezolid is rapidly absorbed after oral dosing with an absolute bioavailability of approximately 100%. Serum half-life is approximately 5.5 hours, and protein binding is approximately 31% [65,66]. Approximately 35% of a 500-mg dose of ^{14}C-linezolid was excreted in urine as the parent drug and 50% as the two major metabolites.

In one study, urinary bactericidal titers of a single oral dose of 600 mg linezolid or 500 mg ciprofloxacin were measured in volunteers [67]. The urinary bactericidal titers of linezolid against gram-positive uropathogens, regardless of their methicillin and fluoroquinolone resistance, could be obtained for at least 12 hours and were comparable to those of ciprofloxacin in fluoroquinolone-susceptible strains, whereas there were no significant urinary bactericidal titers of ciprofloxacin in fluoroquinolone-resistant strains. The urinary bactericidal titers of linezolid have shown that with an oral dose of 600 mg linezolid twice daily, urinary bactericidal activity against gram-positive uropathogens with minimal inhibitory concentration ranges of 1 to 2 mg/L can be expected throughout the complete therapeutic interval [67].

Summary

Antibiotic resistance is an increasing problem in urologic practice. Uncomplicated and complicated—especially nosocomial—uropathogens may exhibit resistance to multiple antibiotics and pose problems for empiric therapy. To choose the right antibiotic for empiric therapy, it is necessary to consider the bacterial spectrum and antibiotic susceptibility of the uropathogens. Each institution must conduct its own local and recent evaluation. To combat the development of antibiotic resistance, a basic understanding of antibiotic action and resistance mechanisms is helpful. In the future, the rate of antibiotic resistance possibly will continue to increase. Strategies to decrease this trend, such as antibiotic policies, must be developed and incorporated in urologic practice.

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